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Full title: Developing a better biopsychosocial understanding of pain in inflammatory bowel disease: a cross-sectional study

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Summary of article: This paper presents biopsychosocial factors associated with pain in inflammatory bowel disease. It demonstrates that emotional, cognitive and behavioural processes are associated with pain even when controlling for sociodemographic and disease-related factors, highlighting key areas for future pain management interventions.

Abstract

Background: Pain is frequently reported by patients with inflammatory bowel disease (IBD). Pain in IBD is not fully explained by disease activity or other clinical findings, and a recent systematic review suggested that psychosocial factors have an important role in IBD-pain. The aim of this study was to investigate psychosocial factors associated with pain in IBD.

Methods: 297 adults (>16 years) with IBD were recruited from outpatient clinics (n=114) and online (n=183). Participants completed validated questionnaires assessing pain and potential emotional, cognitive and behavioural correlates. Socio-demographic and clinical factors including disease activity were also recorded.

Results: 243 (81.8%) of participants reported pain. Of these 243, mean age was 36 years; 153 (63%) had Crohn's disease (CD), 90 (37%) had ulcerative colitis (UC), and 165 (67.9%) were female. 62.6% reported mild, 31.6% moderate and 5.8% severe pain. 40.3% of participants with pain met established criteria for chronic pain and 18.5% reported opioid use. Female gender, smoking, surgery and steroid use were associated with greater pain severity. Psychosocial factors associated with pain-related interference included depression, catastrophising, fear avoidance, lower self-efficacy and worse mental well-being. Regression models explained 45.6% of the variance in pain severity and 49.7% of pain interference. Psychosocial factors explained 9.5% and 24% of this variance respectively when controlling for demographic and clinical variables.

Conclusions: Pain in IBD is significantly associated with cognitive and behavioural factors as well as low mood. This study contributes to a biopsychosocial understanding of pain in IBD and identifies important targets for future interventions.

Key words: Pain, IBD, biopsychosocial

Introduction

Pain is a common symptom in inflammatory bowel disease (IBD) and has a significant impact on quality of life[1]. Attenuating pain is a primary target of IBD medical management; abdominal pain severity is routinely assessed in disease activity indices in clinical practice and serves as a key endpoint in IBD clinical trials[2]. During active disease, over two thirds of patients report pain. However, 42-48% of patients will continue to experience pain, despite clinical and endoscopic evidence of quiescent disease[3]. Abdominal pain is the most commonly reported type of pain in IBD, however extra-intestinal manifestations of pain in IBD can be present in the eyes, skin or joints[1,4]. Pain that is not associated with inflammation, sub-acute obstruction or other disease-related complications in IBD is a clinical challenge, as conventional IBD medical therapy is inappropriate and patients report frustration that pain is not being adequately addressed[5].

Chronic abdominal pain in IBD is frequently categorised as irritable bowel syndrome (IBS)-type symptoms. Abdominal pain is a cardinal feature of IBS, with Rome IV criteria also including altered stool frequency or stool consistency[6]. Thirty-six percent of people with ulcerative colitis (UC) and 46% with Crohn's disease (CD) in remission meet the classification for IBS[7], and a biopsychosocial model of IBS and IBD places these conditions on a functional continuum of gut-brain interactions[8]. However, there is limited evidence to confirm whether key processes and characteristics associated with chronic pain in IBS also apply to IBS-IBD populations. Many treatment approaches in IBS remain untested in the context of IBD-pain. Several key mechanisms identified in IBS and chronic pain research, including positive psychological factors and how individuals respond cognitively and

behaviourally to symptoms, are yet to be explored in IBD-pain. While the primary focus of the present study was not IBS in IBD, the IBS literature informed our approach.

Causes of chronic pain in IBD involve both bottom-up (visceral and peripheral) and top-down (central, neurobiological and psychological) factors[3]. Low-grade inflammation can result in the release of cytokines and other key mediators, leading to visceral hypersensitivity[9]. Pain modulation in IBD is also influenced by central mechanisms; a recent small randomised controlled trial showed the ameliorating effects of transcranial direct current stimulation on several pain outcomes up to one week post treatment[10]. Stress and other psychological processes may exacerbate pain by disrupting descending control mechanisms, gut-brain interactions or microbial regulation, or indirectly through adopting unhelpful coping behaviours[3]. A recent systematic review showed a number of psychosocial factors associated with pain in IBD[11], including depression, anxiety and pain catastrophising, as well as protective psychosocial factors of perceptions of social support and control, which are associated with less pain. Coping styles and perceived stress correlated with pain in a large cohort of adults with CD[12].

Given this complex aetiology, adequate pain management in IBD can be challenging and there is much heterogeneity in interventions tested to date[13]. Chronic opioid use has been shown to increase the risk of hyperalgesia and can lead to deleterious effects on the gastrointestinal tract, including narcotic bowel syndrome and opioid-induced constipation[14]. Treating pain in IBD solely as a biomedical problem can limit therapeutic options and further distress patients. Adjuvant psychological support with medical management in IBD can enable patients to manage symptoms and the emotional impact of the disease[15]. Integrated

148 care models in IBD encompassing psychological support have led to reductions in disease
149 burden and healthcare costs[16].
150
151 Not enough is understood around potentially modifiable factors related to pain in adults with
152 IBD. Preliminary research suggests that psychological processes have an important role in
153 IBD-pain[11,12]. Many previous studies are limited by study design, including limited pain
154 measurement; measures of pain in quality of life or disease activity indices are frequently
155 limited to one item on pain severity. Assessing the impact of pain and pain-specific beliefs,
156 alongside severity, provides a better understanding of chronic or functional pain in IBD[17]. A
157 more detailed understanding of biopsychosocial factors associated with pain in IBD may aid
158 the development of effective interventions[3,11,18]. This has been demonstrated in other
159 gastrointestinal and autoimmune diseases, including IBS[19] and pain in multiple sclerosis
160 (MS)[20].
161
162 Given these considerations, the aims of this study were to i) identify the prevalence and
163 severity of pain in adults with IBD ii) investigate the influence of sociodemographic, clinical
164 and psychological factors in pain severity and pain-related interference in IBD. Psychosocial
165 factors included positive and negative emotional, cognitive and behavioural factors, as well
166 as constructs identified in chronic pain and IBS populations not yet assessed in IBD-pain[11].
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Materials and Methods

Study design and population

An observational cross-sectional study design was used. Data collection took place January to June 2018. The primary outcomes were pain severity and pain-related interference measured by the Brief Pain Inventory[21].

Inclusion criteria were diagnosis of Crohn's disease (CD) or ulcerative colitis (UC) for more than 6 months and 16 years or older. Exclusion criteria included insufficient command of spoken English, diagnosis of indeterminate colitis and inability to provide informed consent. Participants were recruited via outpatient clinics and online; clinic participants were recruited consecutively from three National Health Service gastroenterology outpatient clinics in three London-based hospitals and online participants were recruited via the UK Crohn's and Colitis charity website. Clinic-recruited participants had a clinician-confirmed diagnosis of CD or UC and once consented, completed a paper questionnaire in clinic or at home and then returned their questionnaire by post. Online participants provided consent and completed the questionnaire online (https://www.onlinesurveys.ac.uk/).

Sociodemographic and clinical data collection

The questionnaire included clinical and sociodemographic information, including IBD diagnosis, medication and smoking status, pain medication, pain-related comorbidities, strategies for pain management and classification for chronic pain. This was defined as "pain occurring every day for 3 months within the last 6 months", which has been utilised in previous chronic IBD-pain research[22]. Disease activity (Harvey Bradshaw Index (HBI) for

CD[23] and Simple Clinical Colitis Activity Index (SCCAI) for UC[24] was completed by a clinician or the participant in the clinic and online groups, respectively. A score of < 5 was considered as inactive disease. A stool sample was requested from clinic participants to measure faecal calprotectin, with a score of > 250ug/g used to indicate active disease[25]. Data on IBS and fatigue severity were collected using the IBS symptom severity score[26] and IBD-fatigue questionnaire (Section I)[27].

Study questionnaires

Pain severity and Pain interference

Brief Pain Inventory Short-Form (BPI) was used to assess pain severity and pain interference[21]. Pain severity includes 4 items, including present pain, worst pain, least level of pain and average pain severity in the previous 24 hours, yielding a mean pain severity index score. Pain interference has 7 items, assessing general activity, mood, mobility, work, relationships, sleep and enjoyment of life. A mean severity scoring of 1-3 was classified as mild pain, 4-6 moderate and 7 or more severe pain, using pre-defined cut-offs[28].

Depression

Patient Health Questionnaire-9 (PHQ-9)[29] is a self-report tool for case finding and assessing major depressive disorder. The tool assesses depressive symptoms within the last two weeks, and each item is rated on a 4-point scale reflecting the frequency of the depressive symptom (e.g. 'never' to 'nearly every day'). Scores yield presentation of minimum (PHQ-9 score 0-4), mild (PHQ-9 score 5-9), moderate (PHQ-9 score 10-14), moderate to severe (PHQ-9 15-19) and severe depressive symptoms (PHQ-9 score ≥20).

Anxiety

Generalised Anxiety Disorder-7 (GAD-7) assesses probable cases of an anxiety disorder and symptom severity and shows good reliability and validity[30]. Participants are asked how bothered they have been in the previous two weeks by 7 core symptoms, with response items rated 0-3 ('not at all' to 'nearly every day'). The GAD-7 produces a total score of 21, with mild, moderate and severe levels of anxiety symptoms cut offs standing at ≥5, ≥10, and ≥15, respectively.

Pain Catastrophising

Pain Catastrophising Scale[31] measures the extent to which patients ruminate, exaggerate or magnify the threat of pain sensations. It is comprised of 13-items measuring rumination, magnification and helplessness. Higher scores reflect a greater tendency to catastrophise about pain, with overall scores ranging from 0-52; 30 or more indicates clinical relevance[31].

Cognitive and Behavioural Response to Symptoms

The Cognitive and Behavioural Response to Symptoms Questionnaire (CBRQ)[32] measures 5 cognitive and 2 behavioural subscales. Cognitive subscales include catastrophising, damaging beliefs, fear avoidance, embarrassment avoidance and symptom focusing. Behavioural subscales include all or nothing behaviour and avoidance/resting behaviour. As catastrophising was measured elsewhere (see above), the catastrophising scale was removed. Items are rated on a 5-point Likert-scale ranging from 'strongly disagree' to 'strongly agree'. The overall score is calculated from the total of items within subscales. The CBRQ has been used in different illness populations previously, including IBD[33].

Stress

Perceived Stress Scale[34] assesses participants' appraisals of potential stressful situations within the previous month. Items require participants to indicate how often they have felt, for example, 'unable to cope with all the things you had to do'. Ten items are scored on a 5-point scale, yielding an overall score of 0-40; higher scores indicate greater perceived stress, the extent to which the individual has felt overwhelmed by stressful situations within the last month.

Pain self-efficacy

Pain Self Efficacy Questionnaire[35] assesses participants' belief that they are able to accomplish a range of activities, despite their pain. Participants rate the 10 items on how confident they feel in their ability to carry out tasks (7-point scale; 'not at all confident' to 'completely confident'). For example, 'I can still do many of the things I enjoy doing, such as hobbies or leisure activity, despite the pain'. Total scores range from 0-60, greater scores demonstrating stronger self-efficacy beliefs.

Pain acceptance

Chronic Pain Acceptance Questionnaire (CPAQ-8)[36,37] addresses both activity engagement and 'pain willingness'. Eight items are scored on a 6-point Likert scale from 'never true' to 'always true', greater scores indicating greater acceptance of pain.

Mental well-being

Mental Health Continuum Short-Form (MHC-SF)[38] is a 14-item measure assessing emotional (3 items), psychological (6 items) and social well-being (5 items). It demonstrates excellent internal consistency (Cronbach's alpha >0.8). Items are rated 0-5 from 'never' to 'every day', total scores ranging from 0-70. Individuals who answer 'every day' or 'almost every day' for

at least one of the three signs of hedonic well-being and at least six of the eleven signs of positive functioning are considered to have 'flourishing well-being'. 'Languishing mental health' is considered if an individual has answered low levels ('never' or 'once or twice') to at least one measure of hedonic well-being and at least six measures of positive functioning. Those who don't fulfil either 'flourishing' or 'languishing' mental health are categorised as moderately mentally healthy. Higher scores represent higher levels of mental well-being.

Dietary behaviour

Dietary behaviour was assessed by 4 items: 'I avoid certain food or drinks which I know makes my pain worse'; 'I skip meals or eating to avoid worsening my pain'; 'I tend not to eat out or eat socially because of the risk of making my pain worse'; 'My eating patterns have changed because of my pain'. Cronbach's alpha demonstrated that the four items have high internal consistency ($\alpha = 0.82$). Items are rated from 0-4 (strongly disagree to strongly agree), and higher scores indicate greater impact of pain on dietary behaviour, with scores ranging from 0-16.

Sample size

According to Cohen[39] to test a medium sized multiple correlation with 80% power and a significance level of 0.05, a minimum sample size of 107 participants for a regression model with eight independent variables (parameters) would be required. Adding another ten variables would increase the sample size required to about 160. A larger sample size of approximately 300 was proposed to allow for potential sub-group analyses.

Statistical methods

Missing data were replaced with imputed values using the Multiple Imputation Chained Equation Method (MICE) in Stata version 15. Overall, 15.6% of all values were missing, 92.9% of the variables had at least one missing value and 93.9% of 297 participants had at least one missing value. All variables in the regression model, except for clinical/demographic variables which had no missing data and some variables with high rates of missing data (faecal calprotectin, stoma/ileo-anal pouch, and BPI item 7), were included in the imputation model. Twenty imputed datasets were generated which exceeds the minimum of 10 based on the fraction of missing information [40]. These data were transferred into SPSS for further analysis.

Exploratory variables were described using frequencies, percentages, means and standard deviations. General psychological measures (depression, anxiety, stress, mental well-being) were compared between the Pain and No Pain groups using an independent two groups t-test.

Multivariable regression analyses examined whether psychosocial factors predicted pain outcomes, after controlling for sociodemographic and clinical factors. Significant factors associated with pain severity or pain interference from univariate analyses were entered into a 3-block multiple regression model (1: sociodemographic, 2: clinical and 3: psychological factors). Regression models were fitted to each of the 20 imputed datasets and then combined to produce averaged estimates, overall statistical tests and measures of fit (R^2).

To determine whether the recruitment group (clinic/online) moderated the effect of psychosocial measures on pain severity and interference, the change in fit of the regression model following the addition of the moderating effects to the overall model was tested. If the test of moderating effects was not statistically significant then the data would be analysed as

single sample with recruitment group added to the block 1 explanatory variables (see above) in the regression.

The threshold for statistical significance was set at $p < .05$. Analyses were conducted using SPSS version 25.

Ethical Considerations

This cross-sectional study was approved by the London-Surrey Border Ethics Committee (17/LO/1527). All participants provided consent before taking part and were given a unique study ID to ensure anonymity.

Results

Descriptives

A total of 297 participants completed the questionnaire; 183 CCUK-recruited online participants and 114 participants from gastroenterology outpatient clinics. 28 indicated no pain (summed score of 0 on the BPI Pain Severity) and 269 participants reported some degree of pain (90.6%). 26 participants were removed from the pain group due to incomplete data on pain-specific questionnaires, resulting in 243 participants in the pain cohort for univariate and multivariable analyses. Sociodemographic and clinical data is presented in Table 1. Of the 297 participants, 181 (60.9%) had a diagnosis of CD, 190 (64%) were female and 219 (73.7%) were White-British. Mean age was 36.3 years, with participants on average being diagnosed for 9 years. Mean disease activity score was 6.60 (SD= 5.42) and 4.91 (SD = 3.31) for the HBI and SCCAI, respectively. The most common IBD medication was thiopurines (30.5%).

Insert Table 1. Socio-demographic and clinical profiles of overall cohort, clinic and online participants

Participants with pain

There was a significantly higher proportion of females in the group with pain (67.9% female) compared to the group with no pain (25% female). Participants with pain reported a greater number of flares in the previous 2 years and higher disease activity scores (HBI/SCCAI) compared to those reporting no pain. Mean scores and t-tests for psychological factors (non-pain specific) for the pain and no-pain groups are presented in Table 2.

Mean pain severity scores and other pain-related clinical data for the sample of participants with pain (n = 243) are presented in Table 3. One hundred a fifty-two (62.6%) reported mild pain, 77 (31.7%) reported moderate pain and 14 (5.8%) reported severe pain. The most common self-management strategy for pain was heat (49%), followed by exercise (32.5%). 40.3% of participants reporting pain met the criteria for a chronic pain diagnosis. Abdominal pain was the most common location of pain (88.5%). Half of participants reported low back pain and 39.5% reported headache/migraines. Pain medications are presented in Table 3 with paracetamol (35.4%) and opioids (18.5%) being the most commonly used.
Participants with active disease defined by the HBI or SCCAI reported significantly higher scores on pain severity in both CD and UC ($p < .05$). 75.2% and 75.6% of participants with CD and UC, respectively, scored at least moderate IBS symptom severity. Of the 43 participants with pain who provided a stool sample for faecal calprotectin, 27.9% with quiescent disease reported at least moderate pain.

Overall 27.6% showed ‘languishing’ mental well-being, 31.3% showed ‘flourishing’ mental-health and 41.2% were moderately mentally healthy.

Clinic vs Online participants

Differences were identified between participants recruited via the clinic or online. Disease duration was significantly longer in the clinic compared to the online group (12.5 vs. 8.3 years, p=.001). Number of self-reported flares in the prior 2 years (3.5 vs. 2.4, p<.001) and self-reported disease activity scores (HBI: 8.1 vs. 3.5, p<.001; SCCA: 5.8 vs. 3.7, p<.001) were significantly higher in the online participant group. Significantly more participants in the online cohort were female (71.0% vs. 52.6%, p=.001) and were of White British origin (82.0% vs. 60.5%, p<.001).

Participants recruited online reported significantly higher scores than clinic recruits for pain severity (3.7 vs. 2.7, p = <.001), pain interference (4.4 vs. 3.4, p = .012) and negative psychosocial variables (Supplementary Table 1). A significantly greater proportion of online than clinic participants were on anti-depressants (24.0% vs.13.2%, p=.030), met the classification for chronic pain (48.5% vs. 24.4%, p<.001) and listed co-codamol as their pain medication (17.4% vs. 3.7%, p=.002). Of the online participants with pain, 8.7% and 4.0% of the online cohort had a current stoma or ileo-anal pouch, respectively. There were insufficient data due to missingness to analyse clinic participants with stomas/ileo-anal pouch.

Insert Table 2. Means and standard deviations of pain and general psychological factors in pain and non-pain cohort

Insert Table 3. Pain-related characteristics of overall, clinic and online pain cohort

Univariate analyses

Univariate analyses of sociodemographic and clinical factors associated with pain are presented in Supplementary Tables S2-4. Greater pain severity scores were associated with female gender and previous surgery. Anti-depressant use was significantly associated with pain interference. Steroid use (prednisolone) was significantly associated with greater pain

severity and interference. Azathioprine and methotrexate were significantly associated with greater pain interference. No other IBD medication was significantly associated with pain outcomes. Current smoking, employment and education status were all significantly associated with pain outcomes ($p < .05$). Higher educational attainment and being employed was associated with less pain severity. Dummy variables were created for low educational attainment and unemployed or retired for multivariable analyses. Fatigue significantly correlated with pain severity ($r = 0.49$) and pain interference ($r = 0.42$).

Pearson correlations of psychosocial factors associated with pain are presented in Supplementary Table S4. Pain severity significantly correlated with all psychological factors. Pain interference significantly correlated with all psychological factors, excluding pain acceptance. Greater pain severity and interference were associated with greater impact on dietary behaviour ($r = 0.32$ and $r = 0.39$, respectively).

Multivariable analyses

Collinearity diagnostics revealed significant intercorrelations between some independent regression variables. The final set of independent variables selected for multivariate analyses did not violate multi-collinearity assumptions (VIF <2, condition index < 30).

The addition of the six moderators (effect of recruitment group on the relationship between psycho-social factors and pain) did not improve the fit of either model. In both cases the F-test was not statistically significant (Pain severity: $F[6, 201]=1.16$, $p=.39$, pain interference: $F[6, 201]=1.23$, $p=.29$). Changes in the R^2 were small (Pain severity: 45.6% to 47.4% $\Delta=1.8\%$, Pain interference: 49.7% to 51.5% $\Delta=1.8\%$). A decision was therefore taken to drop the moderating effects whilst retaining source of recruitment in the main effects model.

Multivariable analyses of pain severity and pain interference are presented in Tables 4 and 5 respectively.

For pain severity the addition of psychosocial factors to the regression model containing sociodemographic and clinical factors was statistically significant $F(18, 225) = 9.429$, $p < .001$. Sociodemographic factors explained 17.6% of the variance in pain severity in the overall model. Clinical factors explained an additional 17.9% and psychosocial factors explained a further 9.5% of the variance in pain severity. The overall model explained 45.6% of the variance in pain severity.

For pain interference, the addition of psychosocial factors to the model was statistically significant $F(18, 225) = 11.110$, $p < .001$. Socio-demographic factors explained 8.9% of the variance in pain interference, and clinical factors explained an additional 16.2% of the variance. Psychological factors explained a further 24% of the variance in pain interference. The overall model explained 49.7% of the variance in pain interference.

Table 4 Multivariable regression analyses of socio-demographic, clinical and psychological factors predicting pain severity in pain cohort (n=243)

Table 5. Multivariable regression analyses of socio-demographic, clinical and psychological factors predicting pain interference in pain cohort (n=243)

Discussion

This study aimed to develop a better biopsychosocial understanding of pain in adults with IBD. Results demonstrate that pain is a prevalent problem and that emotional, cognitive and behavioural processes are associated with pain in addition to demographic and disease processes (findings summarised in Figure 1). Psychosocial processes explained an additional 9.5% and 24% of pain severity and pain interference, respectively. Although complete

elimination of pain may not be possible due to the relapsing remitting nature of IBD, targeting potentially modifiable psychological factors related to pain severity and interference may be of value to improve functioning and quality of life.

Over a third of participants with pain reported at least moderate pain severity, and a substantial number of participants had chronic pain and were on anti-depressants. Previous use of the BPI in an IBD population has shown similar distributions for mild, moderate and severe pain[28], however a lower proportion of individuals in this study reported no pain (9.4%). After paracetamol, opioids were the most frequently listed medication for pain, used by 18.5% of individuals with pain. This supports increasing trends of opioid prescription evident in non-cancer pain in the UK[41]. Research demonstrates the adverse effects of prolonged opioid use in IBD, including dose-dependent effects on morbidity and mortality and greater healthcare utilisation[42]. In a US study of Crohn's disease (CD), 37% of patients diagnosed with concomitant functional symptoms were misusing opioid medication, measured by a prescription monitoring programme[43]. Clearer defined prescribing criteria for clinicians and greater awareness and support for patients are vital to reduce use of opioids in IBD.

Emotional factors including depression and anxiety were associated with increased pain severity and interference. Pain is likely a distressing experience for people with IBD. In turn, a top-down affective dimension in pain processing may create a vicious cycle of pain and distress [3]. Although acute stress has a role in buffering noxious input (facilitating a 'fight or flight' response), chronic stress, worrying and hypervigilance may disrupt descending inhibitory control mechanisms, enhancing the experience of pain[3]. A bi-directional association between depression and visceral pain in IBD may be explained by dysregulated signaling along the gut-brain axis[44]. Microbial exposure and regulation in response to

psychosocial stressors is another recognised mechanism explaining the interaction between persistent inflammation and depression[45].

To our knowledge, this is the first study in IBD to show an association between pain and certain positive psychological constructs, namely pain self-efficacy and psychological well-being. Alongside identifying psychosocial risk factors that are anticipated to exacerbate pathology, understanding positive psychological processes may be of equal value in the aim of preventing or reducing pain-related distress and disability[46]. Self-efficacy, defined as an individual's perceived ability to carry out behaviours to meet a goal or outcome[47], is a widely empirically-supported mechanism in the context of adopting new health behaviours, adjusting beliefs or engaging in helpful coping strategies. It has been associated with less impairment and distress in chronic pain[48], and improved outcomes in adult and child IBD populations[49-51]. Greater psychological well-being or optimism may be another important construct in increasing one's likelihood of engaging in helpful coping strategies. In support, levels of gratitude in IBD have significantly predicted lower depression in a longitudinal study[52]. These positive psychological factors may serve as 'resilience mechanisms' facilitating adjustment in chronic illness and buffer the impact of symptoms[53]. Understanding both risk factors and resilience factors in IBD may help to identify patients who exhibit 'low resilience' and may be more likely to develop functional symptoms[46]. Self-efficacy and psychological well-being, among other positive psychological constructs, can be targeted in interventions through building of self- confidence, control and self-management skills.

An association between greater pain and fear avoidance and catastrophising about pain echoes findings in previous IBD studies[11], with the latter shown to predict functional disability in adolescents with IBD[54]. Other cognitive-behavioural responses to symptoms associated with pain identified in this study included symptom focusing, beliefs that

symptoms are sign of damage, all or nothing and avoidance-resting behaviours in response to symptoms, which have not previously been investigated in IBD-pain populations. It is thought that avoidant thoughts and behaviours may lead to the development of chronic pain by an increasing fear of movements and inactivity, leading to disability, lethargy and low mood[55]. All or nothing behaviours refer to cyclical periods of intense activity when feeling well, leading to burn-out, over-exhaustion and prolonged periods of rest. Setting realistic goals for daily activity rather than being governed by symptoms may be a helpful strategy, such as through graded activity and exposure techniques. Identification of pain-specific cognitive and behavioural processes in this study builds on a biopsychosocial understanding of IBD-pain and further identifies important treatment targets for future pain management interventions in IBD.

The lack of association between pain acceptance and outcomes is inconsistent with previous research. Pain acceptance has shown significant associations with resilience and less negative mood in chronic IBD-pain populations[56]. Illness acceptance has been shown to predict personal growth, relationship satisfaction and life satisfaction[57]. Mindfulness interventions, of which acceptance is a key tenant, have shown positive outcomes in IBD-patients with functional abdominal symptoms[58]. A lack of an association in this study may be explained by the use of a chronic pain acceptance questionnaire with a sample who did not all meet chronic pain criteria. Alternatively, it may be that pain acceptance is more strongly associated with improvements in mood and quality of life rather than influencing pain outcomes directly. Both pain and illness acceptance warrant further investigation in IBD.

Female gender, current smoking status and steroid use were significantly associated with pain outcomes, consistent with previous research[11]. Moreover, the study demonstrated significantly greater levels of pain, distress and disease activity in the online-recruited cohort.

This suggests that the online community may be particularly vulnerable and a key target sub-population for an intervention. Recently, a meta-analysis examined the differences in CBT trial results in individuals recruited in clinical services compared to open community recruitment, where participants self-refer to take part in studies[59]. In 53 comparisons of internet-based CBT versus waitlist control, open community recruited populations demonstrated greater reductions in anxiety symptoms, which were partly explained by greater treatment adherence and stricter exclusion of severe depression in open community groups. This, and our study findings, suggest that online self-referring individuals may be more likely to present higher pain and distress, and possibly engage and benefit more from psychological interventions. However, recruiting from an online source only may limit generalisability to a 'clinical' population.

Significant associations between disease activity and pain suggests that disease management should remain a key therapeutic target when pain is reported. However, the use of self-reported indices to measure disease activity in this study may be conflated by affective distress. A recent study showed that 29% of IBD patients with histological and colonoscopy-confirmed quiescent disease were erroneously classified as having active disease through the use of HBI/SCCAI, and fulfilled for Rome III criteria for IBS[60]. Faecal calprotectin was not associated with pain in a sub-set of participants in this study, further highlighting the complex relationship between symptom reporting and pathophysiology in IBD. Inconsistencies between clinical and endoscopic biomarkers of both pain and disease activity in IBD have been highlighted previously[3] and support the use of objective and subjective markers, as well as validated patient report outcomes, to guide clinical decision-making.

An impact of pain on dietary behaviours identified in this study aligns with other work in IBD demonstrating the negative effects of abdominal pain on facets of eating or eating

behaviour[61]. Future studies could explore whether regulating eating behaviours and assisting with smoking cessation helps to improve pain outcomes. Similarly, withdrawal from opioids could be considered. Pain was also associated with IBS severity scores and fatigue, reinforcing an overlap in symptomology[8] and symptom clustering in IBD[62].

The results of this study echo psychological processes identified in IBS and pain associated with other long-term conditions. Gastrointestinal-specific anxiety and illness cognitions have been identified as key mechanisms of treatment in IBS[63]; one study examining the effects of a brief cognitive behavioural therapy (CBT) intervention found a significant decrease in catastrophising, damaging beliefs and fear avoidance measured by the CBRQ[64]. Distress, catastrophising and fear avoidance were significantly associated with pain severity and interference in MS-pain[20]. Similar findings in this study suggest that addressing emotions and pain-specific cognitions and behaviours may be important in reducing pain severity and impact in IBD. These processes underpin techniques used in CBT. CBT has a good evidence base in IBS[65,66] and chronic pain[67] and growing evidence base in IBD, showing improvements in quality of life and other psychological outcomes[68,69].

There are several limitations in this study. Firstly, self-reported disease activity was measured for the online cohort, and this group of individuals may have been self-selecting with pain, whereas participants in clinic were approached consecutively. This may explain the higher scores for disease activity, pain and psychological factors in the online group. Although this study aimed to provide an objective measure of disease activity in clinic-recruited participants, only a small sub-set of participants returned samples, therefore faecal calprotectin levels were not included in the multivariable analysis. This study did not measure sensory testing, mucosal signaling molecules relevant to pain (TRPV1) or other physiological

markers. Finally, the cross-sectional nature of the study limits conclusions regarding the direction of causality between pain and psychological factors.

Future research on pain in IBD should assess pain severity, disability and pain-related beliefs using validated pain tools. Studies of longitudinal design should aim to examine the effects of psychological factors on pain severity and impact over time. Inclusion of objective markers of disease activity and other physiological markers of pain can strengthen further studies in understanding the interaction between psychological, central and peripheral processes.

Insert Figure 1. What does this study add?

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Tables

Table 1. Socio-demographic and clinical profiles of the total sample (n=297)

Patient characteristics	n (%)
IBD diagnosis (CD/UC)	181/116 (60.9/39.1)
Gender (Female/Male)	190/107 (64.0/36.0)
Ethnicity	
White-British	219 (73.7)
Education	
No formal qualifications	11 (3.7)
Vocational qualifications	17 (5.7)
School qualifications	37 (12.5)
Advanced school qualifications	45 (15.2)
University degree	111 (37.4)
Postgraduate degree	70 (23.6)
Marital status	
Married/civil partnership/living with partner	132 (46.3)
Divorced/separated	35 (11.8)
Single	116 (39.1)
Employment status	
Employed full-time	161 (54.2)
Employed part-time	44 (14.8)
Full or part-time education	37 (12.5)
Full-time domestic responsibilities	9 (3.0)
Retired	19 (6.4)
Unemployed	20 (6.7)
Smoking status	
Current smoker	33 (11.1)
Previous smoker	64 (21.5)
Non-smoker	198 (66.7)
Current anti-depressant use	59 (19.9)
Previous surgery	93 (31.3)
IBD medication	
Sulfasalazine	6 (2.0)
5-ASA	96 (32.3)
Azathioprine	98 (33.0)
Mecaptapurine	16 (5.3)
Methotrexate	10 (3.4)
Infliximab	25 (8.4)
Adalimumab	52 (17.5)
Vedolizumab	18 (6.1)
Prednisolone	32 (10.8)
Budesonside	13 (4.4)
Allopurinol	11 (3.7)
	Mean (SD)
Age (yrs)	36.03 (12.71)
Disease duration (yrs)	9.62 (9.93)
No. of flares in prior 2 years	3.04 (2.21)
Disease activity score	
HBI	6.60 (5.42)
SCCAI	4.91 (3.31)

Table 2. Means and standard deviations of general psychological and pain factors in the pain and non-pain cohorts

	Pain Cohort (n = 243)	**No Pain Cohort (n = 28)**	
General psychosocial measures	Mean (SD)	Mean (SD)	**Mean difference, 95% CI, p**
Depression	10.66 (6.97)	4.36 (5.86)	6.3 -8.98 to -3.62, p<.001*
Anxiety	8.28 (5.91)	4.27 (5.26)	4.01, -6.30 to -1.71, p=.001*
Stress	22.88 (7.82)	15.93 (6.37)	6.95, -9.92 to -3.90, p<.001*
Mental well-being	39.11 (15.97)	45.18 (16.14)	-6.07, -0.01 to 12.53, p=.050
Pain-specific measures			
Pain self-efficacy	32.67 (15.65)		
Pain catastrophizing	18.58 (13.06)		
Pain fear avoidance	12.12 (5.41)		
Symptom focusing	12.79 (5.89)		
Embarrassment avoidance	10.44 (6.90)		
All or nothing behaviour	9.78 (5.47)		
Avoidance resting behaviour	13.32 (7.26)		
Pain acceptance	27.16 (5.06)		

*Statistically significant at p<.05

Table 3. Pain-related characteristics of overall pain cohort (n = 243)

Pain-related factors	N (%)
Pain Severity (mean, SD)	3.33 (1.96)
Pain Interference (mean, SD)	4.06 (2.92)
No. of Pain Locations	3.52
Pain severity rating:	
Mild	152 (62.6)
Moderate	77 (31.7)
Severe	14 (5.8)
Chronic Pain Diagnosis	98 (40.3)
Pain Medications:	
Paracetamol	86 (35.4)
Co-codamol	31 (12.8)
Opioid	45 (18.5)
Antispasmodic	12 (4.9)
NSAIDs	11 (4.5)
Pregabalin/Gabapentin	7 (2.9)
Pain-related conditions:	
Low back pain	122 (50.0)
Migraine/Headache	96 (39.5)
Arthritis	51 (21.4)
Fibromyalgia	20 (8.2)

Table 4 Multivariable regression analyses of socio-demographic, clinical and psychological factors predicting pain severity in pain cohort (n=243)

Pain Severity	**Block 1**			**Block 2**				**Block 3**	
	*B***	*95% CI*	ΔR^2	*B***	*95% CI*	ΔR^2	*B***	*95% CI*	ΔR^2
Socio-demographic			**0.176**			**0.179**			**0.095**
			F(6, 225) = 7.818, p < .001			**F(12, 225) = 9.785, p < .001**			**F(18, 225) = 9.429, p < .001**
Age	0.00	-0.021, 0.021		-.002	-0.021, 0.017		0.010	-0.009, 0.029	
Gender (male)	-0.50	-0.76, -0.24		-0.36	-0.83, 0.10		-0.40	-0.83, 0.042	
Unemployed/retired	**1.30**	0.55, 2.03		**0.79**	0.11, 1.47		0.43	-0.22, 1.09	
Low Educational Attainment*	0.49	0.20, 0.79		0.17	-0.35, 0.69		-0.14	-0.65, 0.36	
Current smoker	**0.89**	0.50, 1.28		0.63	-0.073, 1.34		0.55	-0.12, 1.23	
Recruitment Group	**1.08**	0.82, 1.34		0.36	-0.14, 0.85		0.30	-0.19, 0.79	
Clinical									
Diagnosis				-0.30	-0.79, 0.20		-0.25	-0.72, 0.22	
Prednisolone				0.10	-0.60, 0.80		0.12	-0.55, 0.79	
Azathoprine				-0.31	-0.78, 0.17		-0.34	-0.79, 0.11	
Methotrexate				0.38	-0.78, 1.54		0.13	-0.96, 1.23	
Previous surgery				0.28	-0.24, 0.81		0.25	-0.26, 0.75	
DAI score (HBI/SCCAI)				**0.84**	0.61, 1.080		**0.59**	0.35, 0.84	

Psychological									
Depression							**0.056**	0.017, 0.096	
Pain catastrophising							0.009	-0.017, 0.034	
Pain self-efficacy							-0.012	-0.031, 0.008	
Fear avoidance							0.025	-0.021, 0.072	
Damage beliefs							0.042	-0.022, 0.11	
All or nothing							-0.037	-0.083, 0.009	
Cumulative R^2	**.176**			**.355**			**.451**		

*below GCSE educational attainment, ** unstandardised beta, ΔR^2 = R-squared change, significant coefficients highlighted in bold

Table 5. Multivariable regression analyses of socio-demographic, clinical and psychological factors predicting pain-related interference in pain cohort (n=243)

Pain-related interference	**Block 1**			**Block 2**			**Block 3**		
	*B***	*95% CI*	ΔR^2	*B***	*95% CI*	ΔR^2	*B***	*95% CI*	ΔR^2
			.089			**.162**			**.240**
			F(6, 225) = 3.563, p < .001			**F(12, 225) = 5.960, p < .001**			**F(18, 225) = 11.110, p < .001**
Socio-demographic									
Age	-0.01	-0.044, 0.023		-0.015	-0.045, 0.016		.019	-0.008, 0.046	
Gender (male)	-0.33	-1.14, 0.47		-0.20	-0.94, 0.55		-0.13	-0.76, 0.51	
Unemployed/retired	**1.34**	0.24, 2.56		0.78	-0.31, 1.87		0.027	-0.92, 0.97	
Low Educational Attainment*	0.41	-0.46, 1.30		-0.13	-0.97, 0.71		-0.65	-1.39, 0.073	
Current smoker	**1.49**	0.27, 2.71		1.062	-0.086, 2.21		0.55	-0.44, 1.54	
Recruitment Group	**1.14**	0.34, 1.97		0.072	-0.73, 0.87		-0.48	-1.19, 0.23	
Clinical				-0.18	-0.97, 0.61		0.012	-0.69, 0.67	
Diagnosis				0.23	-0.89, 1.36		0.029	-0.94, 0.99	
Prednisolone				-0.31	-1.071, 0.46		-0.46	-1.11, 0.23	
Azathoprine				1.89	-0.074, 3.86		1.12	-0.51, 2.88	
Methotrexate				-0.007	-0.83, 0.82		-0.086	-0.80, 0.63	
Previous surgery				**1.203**	0.82, 1.59		**0.55**	0.20, 0.91	

DAI score (HBI/SCCAI)									
Psychological									
Depression							**0.120**	0.063, 0.18	
Pain catastrophising							0.002	-0.035, 0.038	
Pain self-efficacy							**-0.062**	-0.091, -0.034	
Fear avoidance							0.021	-0.046, 0.089	
Damage beliefs							0.012	-0.080, 0.11	
All or nothing							0.019	-0.048, 0.086	
Cumulative R^2	**.089**			**.251**			**.491**		

*below GCSE educational attainment, ** unstandardised beta, ΔR^2 = R-squared change, significant coefficients highlighted in bold

Figure Legends.

Figure 1. What does this study add?

What do we know already?

- Pain is a common symptom of IBD
- Over a third of people with IBD continue to report pain in remission, defined by clinical and endoscopic markers
- Pain is understood as a biopsychosocial problem, involving neurobiological, peripheral factors and central factors

What does this study add?

- Many patients experience pain which is chronic and report the use of opioids and anti-depressants
- Emotions, cognitions and behaviours are significantly associated with pain severity and pain-related interference in IBD, including pain-specific cognitions and behaviours
- Positive psychological factors, namely pain self-efficacy and positive psychological well-being, are associated with less pain
- Results suggest that addressing emotions and pain-related cognitions and behaviours are important treatment targets for future pain management interventions in IBD